

Surgery in leukemias. Now only a procedure of necessity

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Abstract

Background: Complex participation of spleen in many functions of human body and multiple consecutive pathology, determined in time ever-changing indications of splenectomy especially in the two mainly important clinical scenarios: trauma and hematological disorders. **Patients and method:** In an attempt to identify those patients who benefited from splenectomy in cases with chronic leukemias who had splenic removal to palliate the clinical consequences of megalosplenism or hematologic effects of hypersplenism were reviewed. Demographic informations, clinical, laboratory and operative data together with outcomes of such cases were analyzed. **Results:** Our little series include four men and two women aged between 43 and 51 years diagnosed with hairy cell leukemia - HCL - (n=3), chronic lymphocytic leukemia - CLL - (n=2) and respectively chronic myeloid leukemia - CML - (n=1). In all patients with HCL and one case with CLL, surgery was done for significant splenomegaly, associated with refractory hypersplenism obtaining convenable clinical and hematological results after 2-4 years of follow-up. The other two cases with enlarged spleen and abnormal blood elements without still a preoperative diagnosis, were urgently operated on after a medium blunt abdominal trauma presenting acute abdomen, hemoperitoneum and hemorrhagic shock due to a spleen rupture. Both patients after difficult ablation of massive organomegaly assessed histological typical pattern of chronic lymphocytic and respectively myeloid leukemia. Surgery assured a favourable postoperative immediate recovery but one patients died some month later due to progression of its condition. **Conclusions:** Undoubtedly if splenectomy remain lifesaving in all cases of ruptures of the leukemic spleen, the procedure even ensuring however good palliation of mechanical effects of splenomegaly and cytopenias, become somewhat obsolete in some elective chronic cases

Keywords: Splenectomy, chronic hairy cell, lymphoid and myeloid leukemia, chemotherapy

pathologic ruptures and with great reluctance in some carefully selected forms of disease. [5, 6, 7, 8]

Introduction.

From antiquity to the renaissance the spleen was considered an organ full of mysteries (misterii organum plenum) seat of mood, happiness or emotions but not unavailable for the life, its accidental or deliberate removal being without major consequences. Practiced for wounds or closed traumas splenectomy has been recorded a prohibitive mortality for centuries, the first survival being consigned by N Mathias in Colberg barely in 1678[1]. Until the half of XIX century are reported sporadic tentatives and successes of splenic exeresis practiced for traumas, malaria or unspecified splenomegalies [2]. Toward the 1850s the clinical frame of this pathology realised the first nosologic clarifications so the list of splenectomy indications is substantially extended. Besides traumas is added inflammatory, parasitic, cystic or solid benign and malignant lesions or megalosplenias of different causes in which exeresis of this sick viscus was carried for comfort so being added different hemopathies [3]. Between these have been proposed and realised the first spleen ablations for leukemic syndromes (T Bryant -1866), most of them with temporary results and high morbidity and mortality [4]. Advances in the clinical and nosological definition of leukemias but especially in chemotherapy of these sufferings precised the limits and almost unanim skepticism versus operative treatment of this group of diseases, thus currently splenectomy is indicated only

Patients and Method.

Our series include over three decades spanned 78 splenectomies including trauma, infections/inflammations and cystic lesions of the spleen, portal hypertension, tactical reasons, benign and malignant haematologic diseases, and other pathologies comprising six cases in which spleen removal was dictated for typical leukemics syndromes.

Chronic cases were operated in the first decade of this statistics while the acute has been resolved even in the last period.

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Our own observations it's about 4 men and 2 women between of ages of 43 and 51 (mean 47) years in which clinical and biological status was studied together with diagnostic elements, indications and particularities of surgical treatment as well as the results obtained. In first group were included three cases of hairy cell leukemias (HCL) clinically, hematologically and histopathologically confirmed, treated initially by medical preparats (Cladribine or Pentostatine and biological drugs as Rituxibam or Interferon) which after 12-24 months remission presented recurrence of the condition characterised by the discrepancy between documented withdrawall of bone marrow's aspect and persistence or even augumentation of splenomegaly and thrombocytopeny, elements which finally decided exeresis of the spleen.

The first case observed was a 50-years-old man with a two years history accusing marqued astheny and apparently

isolated 2nd degree splenomegaly with firm consistency. Laboratory findings showed a moderate hypochrome anemia (Hb=9 gm %) and leucocytosis with lymphocytosis (7000/ml). Presence of leukemic cells in peripheric blood smear was suggestive for diagnosis as during this period specific cytoplasmic projections being not yet defining. With a presumptive diagnostic of Banti syndrome a "comfort" splenectomy was practiced pursuing both a symptomatic benefit and a diagnostic specification. Intraoperatively we found a smooth, difuse, enlarged spleen (800 gm) and the microscopic examination showed a monotonous prolife-ration of monocytes accompanied by extreme white pulp atrophy, elements that finally allowed a retro-spective diagnosis of HCL (Fig 1,2). Postoperatively a satisfactory remission of clinical and haematological data was obtained at 3 years after which the patient was lost from the evidence.



Fig 1. Hairy cell leukemia (operative piece)

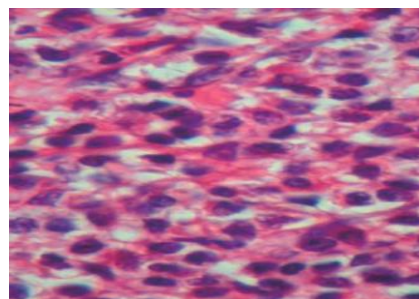


Fig 2. . Hairy cell leukemia microscopical aspect HEx400

The second case also male, aged 47 years has hospitalised for hepatosplenomegaly and peripheral micro-adenopathy, pallor, asthenia, weight loss, sweating and severe pancytopenia. Blood count emphasize some anemia (Ht=11 gm%), leucocytosis (30000/ μ l) and moderate thrombocytopenia (6500/ml). Needle biopsy puncture

signaled a monotonous population of anormal lymphoid cells some with "hairy" cytoplasmatic projections, the diagnosis being précised by medular infiltration of the hairy cells ("honeycomb appearance") and myelofibrosis evidenciated at bone biopsy..(Fig 3).

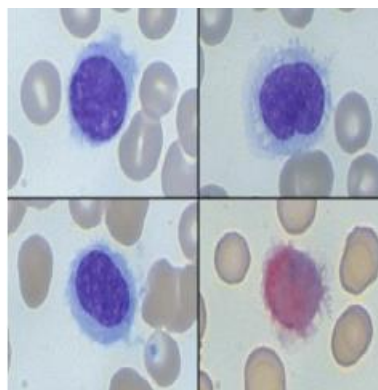


Fig 3. Hairy cell leukemia. Bone marrow (blood) biopsy smear



Fig 4. . Hairy cell leukemia - operative piece.

Ultrasonography showed an increased spleen volume measuring 16 cm both in axial and coronal plans. After a combined Pentostatin and Rituxibam administration for a 4-months period clinical and haematological picture as well as the dimensions of the spleen are less influenced thus the splenectomy is decided and practiced (Fig 4). The spleen weighing 800gm did not show signs of residual lesions but postoperative evolution was favourable, the clinical and blood picture remain stable for a period of three years.

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The third case referred to 45-years-old woman diagnosed clinically and hematologically with chronic lymphocytic leukemia (CLL) where it was achieved a favorable clinical response translated by disappearance of clinical complaints and normalization of hematologic constants after therapy with a Purine analog (Pento-statin). After a period of three years there were still signs of recurrence: progressive reduction of the number of platelets, bone marrow aspirate indicating 10% hairy cells and an enlargement of spleen over the initial dimension revealed by ultrasound examinations. After a new cure of chemotherapy, sonography confirmed the persistence and right progression of splenomegaly and even in absence of another alarming symptoms splenectomy was indicated and practiced. The operative piece weighed 1100 gm. Postoperative evolution was favorable, patient remaining in a prolonged clinical remission for 4 years.

Also we framed between chronic cases a 45 years-old female accusing asthenia and marked fatigability dating about one year which presented a second degree splenomegaly without hepatomegaly or lymphadenopathy. Blood count reveals a hemoglobin of 9 gm/dl, leukocytosis of 45×10^9 per L with 90% lymphocytes and respectively 50×10^9 trombocytes/mm³. Biopsy indicates a bone marrow hypercellularity with presence of mature lymphocytes together with depression of erythropoiesis, granulopoiesis and megakariopoiesis. The diagnosis of chronic lymphatic leukemia has been formulated and chemotherapy started which was interrupted voluntarily after 3 months by the patient. In some month's general condition and biological data deteriorated precipitously together with disturbing increase in spleen volume imposing its comfort exeresis followed by a surprising control of the condition without need of cytostatics or anticorps, prolonged for two years

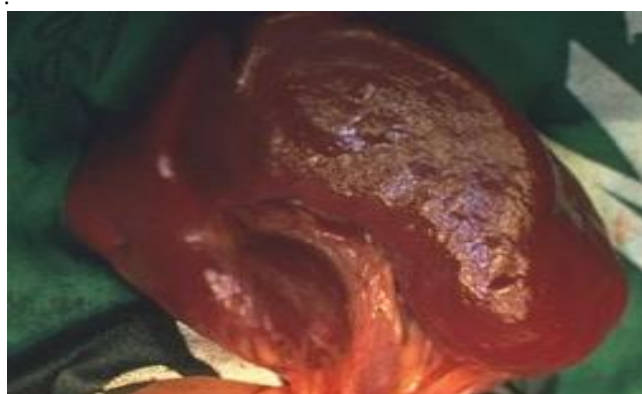


Fig 5. Chronic lymphoid leukemia (operative piece)

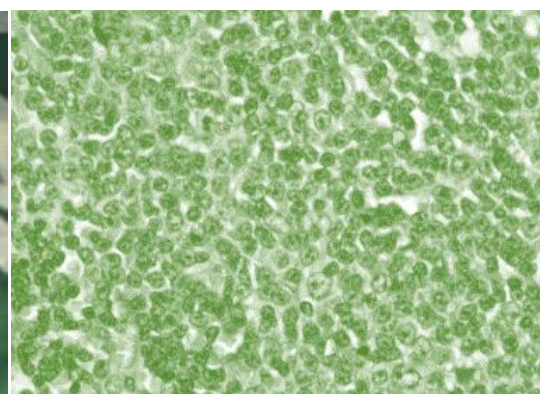


Fig 6. Chronic lymphoid leukemia – microscopic aspect

Finally in two cases splenectomy was practiced emergency imposed by rupture of the pathologic spleen after more or less important abdominal contusions. So a 47 years-old man stands out with a “nonspecific” splenomegaly is admitted by urgency for violent abdominal pains, nausea and vomissements followed by a short loss of conscience, hypotension (blood pressure=90/60 mm Hg) and tachycardia (heart rate=110 bpm). Blood count show hypochrome anemia (Hb=6,5 g/dl), leucocytosis (109), (neutrophils=52%, lymphocytes=16%, basophils=4%, myelocytes=24%, promyelocytes=4%) and respectively 90×10^9 /mm³ platelets. Ultrasonography reveals an important spleno-megaly (18x10

cm) with central irregularities and presence of intrasplenic and left paracolic space fluid. Emergency laparotomy confirmed megasplenism and evidenced rupture of a subcapsular hematoma rupture imposing a difficult splenectomy due to adhesions. Microscopic examination of the viscus objectified presence of micronodules and nests of lymphoid cells interesting the white pulp and the endothelium of trabecular veins confirming the pattern of chronic lymphoid leukemia (LCL). Immunotherapy associated with Fludarabine, Cyclophosphamide and Rituximab, although well tolerated do not prevent progressive deterioration and ultimately the death of patient after one year.

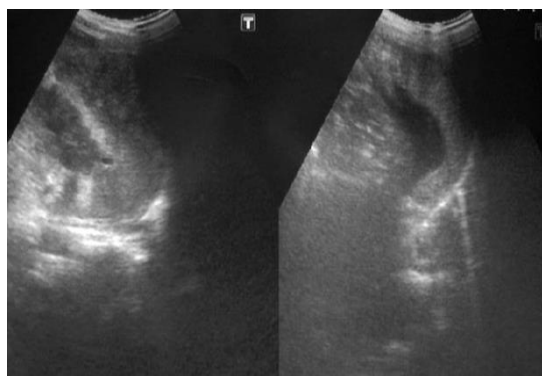


Fig 7. Chronic myeloid leukemia - ultrasonography

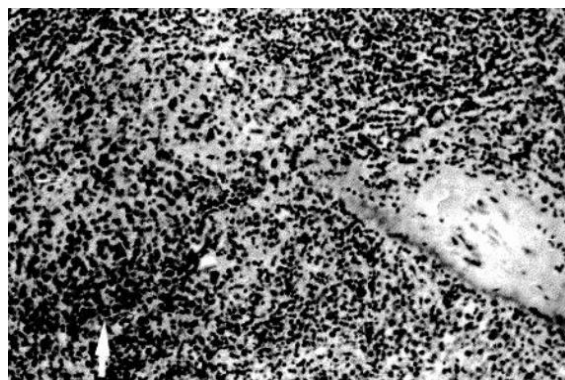


Fig 8. . Chronic myeloid leukemia - microscopic slide

The last case, also male having 40 years, is admitted in emergency unit for sudden instalation of severe pains in the left hypochondrium quickly expanded to the entire abdomen, associating important distension. History do not reveal any special antecedents, patient mentioning only a minor belly contusion after a sudden braking in a crowded tram that spent 48 hours ago. Clinical examination find pallor, hypotension (blood pression=110/70), tachycardia (heart rate=110 bpm), and fever (38,5°). The abdomen shows painful splenomegaly with progressive guarding and contracture. Paraclinic data: Hb=7,5 g/dl, Ht=31%, leukocytes= 24x10⁹ (neutrophils=70%, lymphocytes=3%, eosinophiles=1%, basophils=1%, monocytes=1%, promyelocytes=6%, myelocytes=7%, metamyelocytes=11%), platelets=40x10⁹. Ultrasonography confirmed the presence of free liquid in peritoneum and a second degree splenomegaly with a hypodense central zone (Fig 7). Progression of the compartment abdominal syndrome, anemia, and hemorrhagic shock requires immediate laparotomy which confirmed the important splenomegaly with a central rupture and increasing hematoma together with massive haemoperitoneum, claiming viscus exertion. Operative specimen (1200 g) showed the spleen infiltration with groups of granulocytes and eosinophilic myelocytes specifying the diagnosis of chronic myeloid leukemia (CML), (Fig 8) confirmed also by the aspirate from bone marrow. Postoperatively the patient was subjected to chemotherapy (Imanitib), medication which offered a satisfactory clinical and biological condition followed for 16 months.

Experience with our reduced case series highlights the fact that splenectomy – even though it is not a first-line treatment in most clinical forms of leukemia – this one constituted an effective therapeutic procedure in numerous number of ruptures of pathologic spleen, especially in those of volume disturbing splenomegaly or hematologic repercussions as well as in patients with progressive evolution or refractory after medical therapy.

Discussions.

Our series presents a small number of cases, which emphasizes our restraint to the practice of splenectomy in leukemic syndromes and includes only three conditions HCL (3 cases), LCL (2 cases) and MCL (one case). In four cases surgery was indicated only presence of major clinical components i.e. splenomegaly, hypersplenism associating medullar hyperplasia and cytopenia, failure or recurrence after medical treatment. In the other two cases surgery had a life-saving character being about pathologic spleen ruptures with a clinical picture of acute hemorrhagic shock.

Though somewhat recent entities mentioned in lymphoproliferative syndromes family, the HCL in which splenectomy – despite the magnitude, risks and complications – consensued numerous successes being considered until half of 80's as standard therapy of this lesion. However new therapeutic options as immunotherapy, interferon and especially purine nucleoside analogues, cladribine and pentostatine, have now become first-line therapy realising impressive and durable remission of this leukosis, significantly reducing the number of splenectomies for HCL rare practiced nowadays only for important ruptures or symptomatology, failure or relapse of the disease [12,13,14]. Finally in HCL new therapeutic option consist in purine nucleoside analogs, monoclonal antibody therapy, BTK or BRAF inhibitors, immunotoxins or combination therapy [10, 13]. Today it still remains a valid treatment option in certain cases with huge splenomegaly (spleen Ø > 15 cm or 10 cm

below costal margin and weight > 400 g), but low bone marrow involvement can be an indication for as first-line treatment [15, 16]. Also the option of a laparoscopic technique is actually preferred to the open splenectomy [17].

Chronic lymphoid leukemia is frequently signaled in practice being characterised by lymphocyte accumulation in blood, blood marrow, lymphatic nodes and spleen being often associated with hypersplenism and pancytopenia and eventually with prevalent splenomegaly. This condition is sensible to chemotherapy which assured an optimistic percentage of prolonged survivals. In rare situations in which the marrow is not infiltrated with lymphocytes, splenectomy even in subtotal variant can be proposed with a positive clinical effect on exaggerated discomfort produced by splenomegaly or to potentiate administration of cytostatics or monoclonal anticorps [18,19,20].

Chronic myeloid (granulocytic) leukemia belongs to the group of myeloproliferative syndromes being caused by a specific genetic anomaly appearing to the level of stem cells and characterised by polymorphic symptomatology, asthenia, anemia, anorexia, sometimes important weight reduction, with abdominal discomfort and severe pains due to the zones of splenic infarct, major hyperleucocytosis, trombocytosis but especially important myeloma with presence of myeloid precursors: myeloblasts, promyelocytes, myelocytes, metamyelocytes etc. Myelograms shows a hyperplastic marrow in which granulocyte series is net priority and emphasis of Ph1 chromosome in marrow ponction confirmed the diagnosis. Even if in the past splenectomy was sometimes proposed in CML but today administration of tyrosin kinase inhibitors (Imanitib, Dasatinib, Nilotinib) and allogeneic transplant of bone marrow, imposed as consecrated curative therapy. Splenectomy can be however rarely practiced only in ruptures or multiple splenic infarcts, in cases of spleno-maintenance under condition of optimal treatment as in symptomatic observations with refractory or recurrent evolution. For most authors splenectomy should be avoided, the effects of surgery can be disastrous [22, 23, 24, 25].

Despite the explicite restraints about the opportunity of splenectomy in different varieties of leukemia, we used sporadically appeal in well selected cases and rarely due to necessity, removal of the spleen obtaining satisfactory results characterised by absence of postoperative infections, minimal morbidity with nought mortality and satisfactory survivals. To this also contributed lucid risks analysis especially to the immediat and distant prognosis of every case. So in any patient we evaluated the relation of direct proportionality between the oldness of suffering, spleen volume at clinical and hematological response to splenectomy. Only two of cases with HCL, splenectomy significantly corrected the symptomatology and cytopenia before reaching a critical volume (IIIrd stage) and the respective observations have not requires additional therapy. The evolution of cases with LCL was different, favourable in chronic suffering and respectively rapidly fatal in patient with rupture. Surprisingly the postoperative course of CML occurrence was also satisfactory for a year and a half period [26, 27].

Another considered parameter was the cytopenia provoked by hyperplenism and medullar insuffisance due to leucocyte infiltration and/or precedent chemotherapy founded in four patients. Splenectomy has led to the correction of cytopenia in three of them.

Finally the dispute over the effects of splenectomy referred to the occurrence or not of bone marrow failure seen

in three cases as a brake of cytopenia correction. In these observations medullary insufficiency did not prevent patients to benefiting of surgery and did not find that chemotherapy (2 cases) prevents the remission of disease. In two observations splenectomy not only corrected cytopenia but also improved course condition that it not require complimentary therapy. However in cases of medullary insufficiency, chemotherapy was effective only in one patient.

Personal experience underline actual tendency to reduce the indications of splenectomy to as many as possible conditions and also strengthen the preference for selective treatment, eventually non-operative, of spleen trauma. The prognosis of leukemias for which the spleen is excised appeared different depending of variety and stage of the disease, presence of complications and morbid associations and anterior medical treatment. Splenectomy proven to be more useful in early operated cases (n=3), the surgery patients after a prolonged evolution or after complications benefiting only from symptomatic palliative care, requiring chemotherapy that did not significantly influence prognosis. In our numeric low casuistry three only cases (two with HCL and one with CLL) have been monito-red for 2, 3 and respectively 4 years, surviving in satisfactory condition, two cases (one with HCL and one with CML) were lost of follow-up after few months but the patient with ruptured CLL died after one year.

The usefulness of splenectomy in selected cases of chronic leukemia was however long been disputed being proposed several main indications of organ removal in this pathology as the substantial splenomegaly pressing upon other organs and giving rise to severe abdominal discomfort and the presence of significant hematologic consequences as persistent or increasing WBC, severe anemia, thrombocytopenia or pancytopenia, surgery improving these features and blood profile.

To these conditions added the cases of typical traumatic or delayed ruptures and also of the so called spontaneous and occult ruptures of the leukemic enlarged spleen when its removal is an undoubtedly mandatory and life saving emergency gesture. Symptomatology of these clinical varieties from total absence of any manifestation excluding splenomegaly but also pain, peritoneal irritation, acute anemia, syncope [28, 29, 30].

Although rupture of diseased spleens is uncommon it does carry with a significant risk of mortality. Given the relatively poor sensitivity of the clinical exam for splenomegaly and the ready availability of abdominal US, this imaging modality may be indicated as a screening test in this pathology. Also clinicians need to maintain a supplementary high index of suspicion when faces with abdominal pain in patients with splenomegaly. Splenectomy can also be as an alternative or additional option for symptomatic patients with relapsed or refractory disease. Experience of our numerically reduced series emphasizes that splenectomy even is not a prime-line treatment for rare different clinical forms of leukemia constituted an efficacious therapeutic mean in many cases of pathologic spleen rupture and sometime in patients with disturbing spleen enlargements or severe hematologic repercussions in those with progressive evolution as in ones refractory or recurrent.

Conclusions:

Remaining followers of the current tendency to reduce the indications and number of splenectomy under as

little as possible conditions (including also the non-operative treatment of trauma), our experience is far to be a plea to include the procedure in the therapeutical arsenal of some varieties chronic leukemias. In support of the paradigm of evidence-based medicine we consenned this procedure in few situation only as an extreme resource in outstanding cases used by necessity.

Conflict of Interest. Authors have no conflict of interest to disclose.

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